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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,595	11/30/2005	John Ong	0501US-UTL1	2750

44638 7590 02/20/2009

Intellectual Property Department
Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
02/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,595	ONG ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *11-14 and 35-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 15-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final rejection filed on November 04, 2008 is acknowledged. Claims 1-50 are pending in this application. Applicant elected with traverse Group I (claims 1-10 and 15-34) and elected species exendin-4 (SEQ ID NO:2), poly-arginine for cationic poly-amino acid, tonicifying agent for the agent, hydroxypropyl methylcellulose for viscosity-increasing agent, carbomer for bioadhesive agent, phenylethyl alcohol for preservative, and weight loss for the disease to be treated in the reply filed on May 28, 2008. The traversal was not found persuasive, and the restriction requirement was deemed proper and made FINAL in the previous office action. Claims 11-14, 35-50 remain withdrawn from further consideration, as being drawn to nonelected invention and species. Claims 1-10 and 15-34 are examined on the merits in this office action.

This application contains claims 35-50 drawn to an invention nonelected with traverse in the reply filed on May 28, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objection and Rejection

1. Objection to the title is hereby withdrawn in view of Applicant's amendment to the title to "Methods and Compositions for Enhanced Transmucosal Delivery of Peptides and Proteins".

2. Objection to claim 1 is hereby withdrawn in view of Applicant's arguments.

3. Objection to claim 8 is hereby withdrawn in view of Applicant's amendment to the claim.

4. Objection to claims 27 and 31 are hereby withdrawn in view of Applicant's amendment to the claims.

5. Objection to claims 19-21 are hereby withdrawn in view of Applicant's arguments.

6. Rejection of claims 22-26 under 35 U.S.C. 112, second paragraph, as being indefinite, is hereby withdrawn in view of Applicant's amendment to the claims.

7. Claims 1-10 and 15-34 provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-13, 18-26, 29-33 and 36-38 of copending Application No. 11/034,706 is hereby withdrawn in view of Applicant's arguments.

8. Claims 1-10 and 15-34 provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-13, 18-26, 29-33 and 36-38 of copending Application No. 11/628,123 is hereby withdrawn in view of Applicant's filing of terminal disclaimer .

Maintained Rejection

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Rothbard et al (US 2002/0009491 A1).

11. Rothbard et al teach a pharmaceutical composition comprising components (delivery-enhancing transporter (poly-arginine) and biologically active agents (such as peptide or protein)) in a suitable medium, such as water or a buffered aqueous solution (see paragraphs [0026], [0038] and [0123]). Since the bioactive peptide and cationic polyamino acid are formed in water or aqueous buffer, this would inherently have the functionality and the characteristics of the instantly claimed invention.

Response to Applicant's Arguments

12. Applicant argues that "Rothbard does not disclose a composition where the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition…these components necessarily have opposite net charges at the pH of the composition.:

13. Applicant's arguments have been fully considered but have not been found persuasive. Claim 1 recites, "...wherein at the pH of the composition said compatible buffer does not cause precipitation of the cationic polyamino acid and has a mono-anionic or neutral net charge...wherein the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition..." A mono-anionic charge would leave a -1 charge. A neutral net charge would leave a charge of "0". As the Applicant indicated, the Rothbard reference teaches a composition where the components necessarily have opposite net charges at the pH of the composition, meeting the limitation of neutral net charge. Furthermore, as indicated in the indefiniteness rejection below, it is unclear how a peptide or protein of interest would have the same net charge as the cationic polyamino acid, if the cationic polyamino acid, is for example, 13mer poly-arginine. This would give a +13 charge. For exendin-4, having the sequence HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS, there are not enough positively charged amino acids to give a net charge of +13. Additionally, this peptide has 4 positively charged amino acids (H, K, R and K) and 6 negatively charged amino acids (E, D, E, E, E, E), giving a net charge of -2 on the peptide. Therefore, the reference meets the limitation of claim 1.

14. Claims 1-4, 6-7, 9-10, 15-16 and 18-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Defelippis et al (WO 02/098348, filed in the IDS).

15. Defelippis teaches a composition comprising a GLP-1 compound and a basic polypeptide (see claim 1). Defelippis specifically teaches the use of exendin-4 (see

claim 8, page 12, lines 6-21) as the GLP-1 compound. Defelippis teaches polyarginine as the basic polypeptide (see claim 13). Further, Defelippis teaches that the composition is in a buffered solution (see page 27, lines 18-20) and teaches solutions for injection (see page 31, lines 7-10). This meets the limitation of claims 1, 7 and 9-10. Defelippis teaches the use of a zinc solution at pH of between about 5 and about 6 (see page 29, lines 29-32) and also teaches pH adjustments to less than 5 (see page 31, lines 14-15) and the use of an acetate buffer (see page 29, lines 23-24), meeting the limitations of claims 2-4. Further, Defelippis teaches that use of sucrose (see page 33, line 2) in the composition, meeting the limitation of claim 15. Additionally, Defelippis teaches the use of starch (see page 35, line 1) in the composition, and the use of phenol (see page 31, line 1) and the use of in the composition, meeting the limitations of claims 6, 16 and 18. The instant specification discloses that "exemplary viscosity-increasing and bioadhesive agents that may be used in the compositions discloses herein, include, but are not limited to cellulose derivatives...starch, gums, carbomers, and polycarbophil..." (see paragraph [0210] of instant specification US 2006/0172001 A1). Since bioadhesive includes starch, which is disclosed by Defelippis reference, this meets the limitation of claim 6. Since the reference teaches the composition comprising poly-arginine peptide, exendin-4, and buffer at pH of the instant claims, the composition would inherently have the same functionality and characteristics as the instant composition. Therefore, the composition of the reference would increase the absorption by at least 2 fold, at least 5 fold, and at least 10 fold, meeting the limitations of claims

19-21. Therefore, Defelippis meets the limitations of claims 1-4, 6-7, 9-10, 15-16 and 18-21 of the instant claims.

16. Claims 1-4, 6-7, 9-10, 15-16 and 18-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Defelippis et al (WO 02/098348).

17. The teachings of Defelippis is described, supra. Therefore, Defelippis teachings meet the limitations of claims 1-4, 6-7, 9-10, 15-16 and 18-21 of instant application.

Response to Applicant's Arguments

18. Applicant argues that "Defelippis disclose a composition at a pH where the polyamino acid is precipitated, since it is disclosed as being in particle form, whereas the present claims require that the buffer does not cause precipitation of the cationic polyamino acid."

19. Applicant's arguments have been fully considered but have not been found persuasive. Defelippis reference teaches a composition at the same pH (about pH 5.0 to about 6.0 and below 5.0) comprising poly-arginine and Exendin-4 and the use of acetate buffer. Since the reference teaches the composition comprising the same components as the instant claims, the composition would inherently have all of the functionality and characteristics as the instantly claimed pharmaceutical composition. Further, the bioactive peptide (exendin-4) would have the same net charge as the cationic polyamino acid at the pH of the composition. The reference teaches that the amount of the exendin solution and the basic peptide solution can be mixed together

may be adjusted on the concentration of the therapeutic peptide compound and the basic polypeptide and the buffered zinc acetate or zinc chloride solution is at pH of between about 5 and about 6 can be added to the peptide/basic polypeptide suspension (see p. 29, lines 29-32 and p. 31, lines 14-15). The reference teaches the same composition in the same pH range as instant claims, therefore, the composition inherently has the same characteristic as the instant claims. Therefore, the reference anticipates the instant claims 1-4, 6-7, 9-10, 15-16 and 18-21.

35 U.S.C. 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1-10 and 15-26 rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al (US 2003/0087820 A1, filed in the IDS) in view of Baichwal AR (US Patent No. 5,330,761) and Ryser et al (US Patent No. 4,847,240, filed in the IDS).

24. Young discloses a pharmaceutical composition for using exendin-4 for transmucosal administration (see paragraph [0188]) using an acetate/glutamate buffer (comprises acetic acid/glutamic acid), with a pH in the range of 3-7 (see paragraph [0203]) and further ingredients including mannitol (tonicifying agent), m-cresol (preservative), methylcellulose (viscosity-increasing agent) and other excipients as needed, such as sodium chloride (see paragraph [0203]). Young teaches that the dosage forms preferably include approximately 0.005 to about 5%, of the active ingredient in an aqueous system along with approximately 0.02 to 0.5% (w/v) of an acetate, phosphate, citrate or glutamate or similar buffer either alone or in combination to obtain a pH of the final composition of approximately 3.0 to 7.0 (see paragraph [0203]). This meets the limitation of claims 1-5, 6 in part, 9-10, 15-16, 18-24 and 26. The difference between the reference and the instant claims is that the reference does not teach a bioadhesive agent and the polyarginine and the range of molecular weights of

the polyamino acids, tonicifying agent, viscosity-increasing agent, bioadhesive agent and preservative (Young's ranges overlap the instantly claimed ranges).

25. However, Baichwal AR teaches that a bioadhesive controlled-release solid dosage forms adhere to mucosa (especially in the oral cavity, but also e.g. in periodontal pockets, surgical wounds etc) to provide controlled release of analgesics, anti-inflammatories, anti-tussives, hormone, antibiotics, etc. Further, Baichwal teaches that the bioadhesive controlled release excipients are directly compressible into tablet formulations which are not absorbed into body but provides a localized effect (see basic abstract enclosed).

26. Further, Ryser teaches that it is well known that many molecules of a wide variety are not transported, or are poorly transported, into living cells. Macromolecules, for example, such as proteins, nucleic acids, and polysaccharides are not suited for diffusion or active transport through cell membranes simply because of their size (see column 1, lines 22-27). Ryser teaches that cationic polypeptides, and in particular polyarginine effect or enhance cellular uptake of molecules which are either excluded from or are poorly taken up by cells (see column 1, lines 48-65 and column 4, lines 12-12-18). Ryser teaches that for some proteins as much as a factor of several hundred fold and dramatically increases cellular transport of molecules such as drugs co-factors nucleotides and nucleotide analogs, gaining a very important advantage by using selected cationic polymers, such as poly-L-lysine and poly-L-arginines, which are excellent substrates for physiological proteolytic enzymes present in mammalian cells, i.e. after having served as a transport carrier, they can be digested or otherwise broken

down inside the cells into normal physiologic by-products (see columns 3-4, specifically, column 4, lines 29-34). Ryser further discloses that there are wide variety of molecules which can be covalently bonded to cationic polymers including, peptides and that typically the positively charged groups are primary, secondary, or tertiary amines which ionize at or around neutral pH (the range claimed to prevent precipitation), and that cationic poly(amino acids) are preferred because of the outstanding enhancement in cellular uptake which they provide along with the digesting by proteolytic enzyme some poly(amino aid), i.e. polyarginine, provide (see columns 5-6). Ryser teaches that polycationic amino acids have multiple uses including chemotherapeutic applications, anti-microbial application, for genetic diseases, enhancing cellular uptake or polypeptide hormones, such as insulin, cellular transport for other molecules having biological functions (see columns 15-16).

27. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Young, Baichwal and Ryser for the express benefits for enhancing cellular uptake of polypeptide hormones across membranes, for controlled release, and for the adhesion of the bioactive agents to the mucosa of the patient population (oral cavity, etc). Young reference indicates that delivery of peptide drugs is often difficult because of factors such as molecular size, susceptibility to proteolytic breakdown, rapid plasma clearance, peculiar dose-response curves...and the tendency of peptides and proteins to undergo aggregation, adsorption, and denaturation. Thus, there continues to exist a need for the development of alternative methods to the inconvenient, sometimes painful, injection for administration of peptide drugs (i.e., better

transmucosal routes of administration is necessary because the properties of peptides and proteins make them difficult to utilize) (see paragraph [0009]). One of ordinary skill in the art would have been motivated to combine the teachings since Ryser teaches that cationic polypeptides (polyarginines) enhance the cellular uptake of molecules which are either excluded from or are poorly taken up by cells (some proteins as much as by a factor of several hundred fold and dramatically increased cellular transport of molecules), and Baichwal teaches that addition of bioadhesive enhances the controlled release and adhesion of the bioactive molecules to the mucosa. There is a reasonable expectation of success, since Ryser teaches the enhancing the cellular uptake of protein hormones or polypeptide hormones, such as insulin, and Baichwal teach the controlled release and mucosa adhesion of wide variety of different types of drugs, including analgesics, anti-inflammatory agents, anti-tussive agents, hormone, antibiotics, antacids, anti-viral agents, etc (see claim 3).

28. Furthermore, in regards to the ranges, the MPEP states the following: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."* *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference

process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*"); *In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. Denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Therefore, there is a motivation to optimize since the normal desire of scientist is to improve upon what is already known through routine optimization, with the reasonable expectation that optimization of the known ranges would at least lead to a optimal compound that would lead to optimal treatment conditions.

Response to Applicant's Arguments

29. Applicant argues that "Young does not disclose a cationic polyamino acid at all, nor that the cationic polyamino acid has the same net charge as peptide or protein of interest. Young is also directed to providing exendins and agonists to the blood plasma through various means." Applicant further argues that "Baichwal discloses a tablet formulation containing active ingredient that is not absorbed into the body but instead

provides localized effect. The solid dosage form is bioadhesive when placed in contact with a mucous membrane." Furthermore, Applicant argues that "Ryser is not properly combinable with Young because combining Ryser with Young changes the principle of operation of Young."

30. Applicant's arguments have been fully considered but have not been found persuasive. The prior arts combined are prima facie obvious over the instant claims. Young discloses a pharmaceutical composition for using exendin-4 for transmucosal administration (see paragraph [0188]) using an acetate/glutamate buffer (comprises acetic acid/glutamic acid), with a pH in the range of 3-7 (see paragraph [0203]) and further ingredients including mannitol (tonicifying agent), m-cresol (preservative), methylcellulose (viscosity-increasing agent) and other excipients as needed, such as sodium chloride (see paragraph [0203]). It was indicated in the body of the rejection that difference between the reference and the instant claims is that the reference does not teach a bioadhesive agent and the polyarginine and the range of molecular weights of the polyamino acids, tonicifying agent, viscosity-increasing agent, bioadhesive agent and preservative (Young's ranges overlap the instantly claimed ranges). Baichwal teaches a bioadhesive controlled-release solid dosage forms adhere to mucosa (especially in the oral cavity, but also e.g. in periodontal pockets, surgical wounds etc) to provide controlled release of analgesics, anti-inflammatories, anti-tussives, hormone, antibiotics, etc. Ryser teaches the function of cationic polypeptides that increases the cellular uptake of the therapeutic molecules. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings and formulate a therapeutic

composition for enhanced delivery of the therapeutic agent by associating the agent to a component that enhances the cellular uptake of the agent that is also digested *in vivo*. Young teaches a transmucosal administration and Baichwal teaches an adhesive used for mucosal membrane, therefore, one of ordinary skill in the art would have been motivated to try the combination of the two, for the same purpose of delivering the therapeutic composition via transmucosal administration. Since Young teaches a transmucosal administration, one of ordinary skill in the art would have been motivated to combine the teachings of Young and Ryser for enhancing the cellular uptake of the therapeutic agent via transmucosal administration. Furthermore, one of ordinary skill in the art would have been motivated to combine the teachings and adapt the teachings for the current purpose in view of current teachings in pharmaceutical formulations. Therefore, the combined prior arts are *prima facie* obvious over the instant claims.

New Rejection

35 U.S.C. 112, 2nd

31. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

32. Claims 1-10, 15-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

33. Claim 1 recites, "...wherein at the pH of the composition said compatible buffer does not cause precipitation of the cationic polyamino acid, and has a mono-anionic or

neutral net charge; and wherein the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition..." It is unclear how a bioactive peptide or protein of interest will have the same met charge as the cationic polyamino acid. For example, if the poly-arginine is a 13mer, this would give a net charge of +13. It is unclear how a bioactive peptide or protein, exendin-4, having a 39 amino acid would have a net charge of +13. The sequence of exendin-4 is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS. There are not enough positively charged amino acids (K, R and H) to get the same net charge of +13 as the cationic polyamino acid. Furthermore, it is unclear how a cationic polyamino acid would have a mono-anionic charge or a neutral net charge, when the cationic amino acid would have a + charge. Because claims 2-10, 15-21 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

34. Claim 22 recites, "...said compatible buffer does not cause precipitation of the cationic polyamino acid and has a mono0anionic or neutral net charge; and wherein the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition..." It is unclear how a bioactive peptide or protein of interest will have the same met charge as the cationic polyamino acid. For example, if the poly-arginine is a 13mer, this would give a net charge of +13. It is unclear how a bioactive peptide or protein, exendin-4, having a 39 amino acid would have a net charge of +13. The sequence of exendin-4 is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS. There are not enough

positively charged amino acids (K, R and H) to get the same net charge of +13 as the cationic polyamino acid. Furthermore, it is unclear how a cationic polyamino acid would have a mono-anionic charge or a neutral net charge, when the cationic amino acid would have a + charge. Because claims 23-26 depend from indefinite claim 22 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

35. Claim 27 recites, "...wherein the exendin-4 has the same net charge as the poly-arginine at the pH of the composition." It is unclear how a bioactive peptide or protein of interest will have the same met charge as the cationic polyamino acid. For example, if the poly-arginine is a 13mer, this would give a net charge of +13. It is unclear how a bioactive peptide or protein, exendin-4, having a 39 amino acid would have a net charge of +13. The sequence of exendin-4 is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS. There are not enough positively charged amino acids (K, R and H) to get the same net charge of +13 as the cationic polyamino acid. Because claims 28-30 depend from indefinite claim 27 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

36. Claim 31 recites, "...wherein the exendin-4 has the same net charge as the poly-arginine at the pH of the composition." It is unclear how a bioactive peptide or protein of interest will have the same met charge as the cationic polyamino acid. For example, if the poly-arginine is a 13mer, this would give a net charge of +13. It is unclear how a bioactive peptide or protein, exendin-4, having a 39 amino acid would have a net charge

of +13. The sequence of exendin-4 is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS. There are not enough positively charged amino acids (K, R and H) to get the same net charge of +13 as the cationic polyamino acid. Because claims 32-34 depend from indefinite claim 31 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Conclusion

37. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Cecilia Tsang/
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